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EDITORIAL

Invasive fungal infections in non-neutropenic patients

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Critically ill patients, particularly those with features of immunosuppression, are susceptible to invasive fungal infections (IFI), which pose significant diagnostic and therapeutic challenges [1]. Candida and Aspergillus, the two most prominent fungal pathogens in this population, will be the focus of this short review.

Invasive candidiasis

Invasive candidiasis (IC) refers to systemic infections by yeasts belonging to the genus Candida. *C. albicans* remains the dominant strain, but the epidemiology of IC is changing towards an increase of non-*albicans* strains [2], driven in part by exposure to antifungals [3]. IC can manifest as candidemia or deep-seated (visceral) candidiasis, the latter arising either from hematogenous dissemination or direct inoculation into sterile sites. These two presentations can occur simultaneously or independently.

Risk factors include immunosuppression (including but not limited to neutropenia); the disruption of anatomical barriers by central venous catheters, surgery (particularly abdominal surgery with anastomotic leakages), burns and trauma; parenteral nutrition; known Candida colonization (especially if multifocal); and exposure to broad-spectrum antibiotics.

Clinical manifestations are non-specific, ranging from mild fever to full-blown septic shock.

The diagnosis of IC is difficult. Proven IC is defined by the isolation of *Candida* spp. from sterile sites: from at least one blood culture obtained by venipuncture (not from a catheter) in candidemia, and from specimens collected in a sterile manner from an abdominal, mediastinal, or pleural space or abscess/empyema in deep-seated IC [4, 5]. Blood cultures suffer from a slow turnaround time (2–3 days) and a low sensitivity: while they are sensitive at detecting viable Candida in the bloodstream, they remain negative in deep-seated candidiasis without candidemia, and thus have an overall sensitivity of ~ 50% over the spectrum of IC.

The diagnosis of probable IC relies on the association of risk factors, compatible clinical or radiological manifestations, and mycological evidence obtained through non-culture diagnostics [4, 5]. Among these, the most widely used is the beta-D-glucan (BDG) assay, which detects fragments of the fungal cell wall. It has a low specificity, but its sensitivity (74–86% [6]) may be high enough to rule out IC in settings where the prevalence is low (negative predictive value > 95% [7]). Its specificity can be improved if two consecutive positive results and/or if high threshold values are considered. It can be used in conjunction with the mannan antigen (Mn-Ag) and anti-mannan antibodies (Mn-Ab), which should be assessed in combination for optimal diagnostic performance [8]. More recent molecular tests, including the T2 magnetic resonance assay (for the detection of Candida on whole blood) and polymerase chain reaction (PCR)-based tests (some of which must be carried out on positive blood cultures for optimal sensitivity) have been reported to have good diagnostic performance, but their utility has not been confirmed in large-scale clinical studies. Overall, the diagnostic performance of non-culture tests varies widely across studies focusing on different types of IC (candidemia vs. deep-seated candidiasis, proven vs. probable IC), patient populations, commercial kits and accepted positivity cut-offs, etc., and there remains widespread uncertainty about their optimal clinical use.

The main difficulty in clinical practice lies in the facts that the prevalence of proven IC is usually low (even in patients deemed 'high-risk') [7], but the mortality associated with delayed appropriate treatment is high [9].

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Excluding patients with overt immunosuppression (especially neutropenia), empirical antifungal treatment (EAT) should be considered in patients with multiple risk factors of IC who have persistent fever of unknown source/microbiology while on broad-spectrum antibiotics [10]. Several risk prediction models can be used to identify these high-risk patients, in addition to non-culture-based diagnostics of IC and the results of cultures from non-sterile sites. EAT should be promptly administered in patients with these risk factors if they are in septic shock [10]. Pre-emptive antifungal treatment (i.e., based solely on the positivity of biomarkers) is not advised because fungal biomarkers have a low positive predictive value [11]. However, biomarkers can be used for early cessation of EAT (e.g., repeated negativity of BDG, either alone [12] or in combination with Mn-Ag/Mn-Ab [13]).

In critically ill patients, echinocandins should be the first-line treatment of proven, probable or suspected IC [10]. All four echinocandins (caspofungin, micafungin, anidulafungin, and rezafungin) are fungicidal and exhibit broad-spectrum activity [10, 11]. Echinocandin-resistance is generally rare, but has been reported in *C. glabrata, C. parapsilosis* (which naturally presents higher minimum inhibitory concentration [MIC] values for the echinocandins than other species), and *C. auris* [14]. Fluconazole can be used empirically in patients who are not critically ill and who are considered unlikely to have a fluconazole-resistant Candida species; or for de-escalation from an echinocandin after clinical improvement and confirmation of azole-susceptibility. Fluconazole-resistance is intrinsic in *C. krusei*, increasing in *C. glabrata*, and also present in *C. parapsilosis* and *C. tropicalis* [15]. *C. auris* is an emergent pathogen responsible for nosocomial outbreaks, is often multidrug-resistant, and has been associated with a high mortality (30–60%) [16]. Consequently, species identification and antifungal susceptibility testing should be obtained whenever possible. A thorough diagnostic workup is necessary to exclude secondary foci of infection, including assessment for infective endocarditis, endophthalmitis, suppurative thrombophlebitis and intra-abdominal abscesses, and repeated blood cultures. Echinocandins have limited diffusion in the central nervous system (CNS), eye and urinary tract; recommended agents include liposomal amphotericin B (or azoles) for CNS infections, azoles (or systemic liposomal amphotericin B and/or intravitreal injection of amphotericin B deoxycholate) for ophthalmic infections, and azoles (or amphotericin B deoxycholate) for urinary tract infections (UTI) [10]. Source control, including the prompt removal of indwelling catheters, is mandatory.

Invasive aspergillosis

Aspergillus is a filamentous fungus potentially invading any organ or tissue. With the lung being the predominant portal of entry, approximately 90% of invasive aspergillosis (IA) cases involve invasive pulmonary aspergillosis (IPA) or tracheobronchial aspergillosis (TBA) [17]; hence, the focus of this short review. Traditionally, IPA was considered a disease nearly exclusively affecting immunocompromised patients. It became increasingly clear, however, that IPA may threaten a spectrum of non-neutropenic patients admitted to the intensive care unit (ICU) [18]. Therefore, suspicion for IPA should raise in the face of ICU patients with specific risk factors (see below) and compatible signs and symptoms (i.e., persisting or relapsing fever while on antibiotics, pleuritic rub or chest pain, dyspnea, hemoptysis, or worsening respiratory insufficiency despite antibiotic therapy and ventilator support).

A definite IPA diagnosis requires histopathological evidence combining positive mycology with tissue invasion. However, lung biopsy may be avoided because of coagulopathy and hemodynamic or respiratory instability. This necessitates diagnosis by probable IPA criteria. Following clinical suspicion, a non-definite diagnosis of IPA is based on the presence of supplementary elements adding to the likelihood of IPA, including the presence of ICU risk factors, medical imaging, and mycology [19]. ICU risk factors include solid tumors, uncontrolled human immunodeficiency virus (HIV) infection, decompensated cirrhosis, moderate-to-severe chronic obstructive pulmonary disease (COPD), influenza, and coronavirus disease 2019 (COVID-19) [4, 18, 20, 21]. Importantly, these criteria were designed for including patients in trials with the need for strict thresholds; clearly, IPA cannot be ruled out in the absence of these risk factors. Corticosteroids deserves a special note. While prolonged use is considered a host factor contributing to immunosuppression, short-term use during critical illness is less recognized as a clear trigger. The current advice is to avoid corticosteroids in patients with influenza, while in COVID-19 patients the benefits of corticosteroids outweigh the presumed risk for IPA [20, 21].

A probable IPA diagnosis requires a chest computed tomography (CT) indicating pulmonary infiltrates or cavitary lesions. Infiltrates with a halo sign or air-crescent sign are very indicative for invasive fungal disease but rare in non-neutropenic patients. The diagnosis of probable TBA requires a bronchoscopy confirming presence of either tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar [4].

Finally, mycological criteria may include either an Aspergillus-positive culture or a positive galactomannan test (≥ 1.0 optical density index) on fluid from

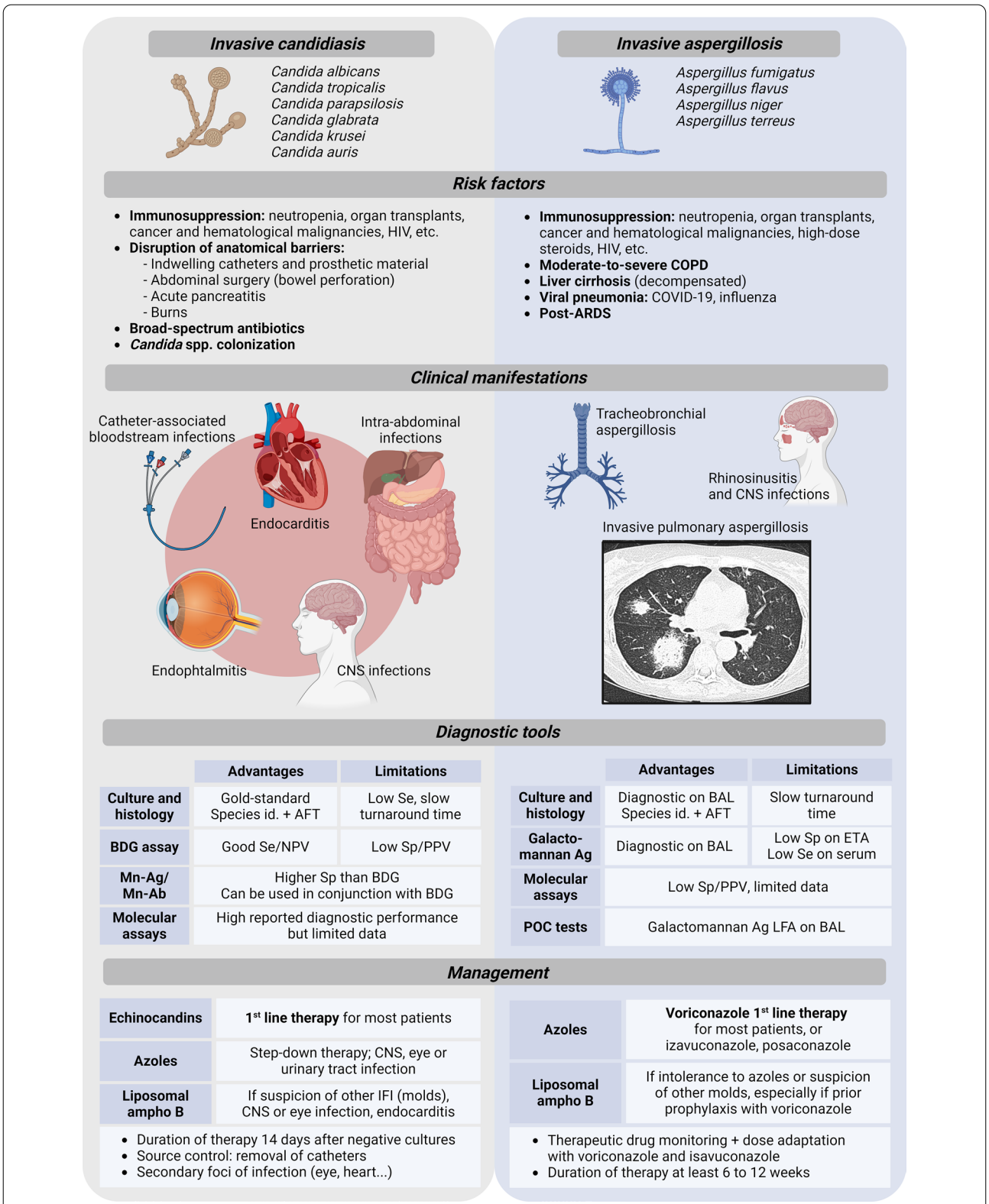

Fig. 1 Overview of the risk factors, clinical manifestations, diagnostic workup and management of invasive candidiasis and invasive aspergillosis in ICU patients. *AFT* antifungal susceptibility testing, *Ag* antigen, *BAL* bronchoalveolar lavage, *BDG* beta-D-glucan, *COPD* chronic obstructive pulmonary disease, *CNS* central nervous system, *COVID-19* coronavirus disease 2019, *ETA* endotracheal aspirate, *HIV* human immunodeficiency virus, *IFI* invasive fungal infections, *LFA* lateral flow assay, *Mn-Ab* anti-mannan antibodies, *Mn-Ag* mannan antigen, *NPV* negative predictive value, *PPV* positive predictive value, *Se* sensitivity, *Sp* specificity, *Species id.* species identification. Figure created with BioRender

bonchoalveolar lavage (BAL) [4]. A positive galactomannan test on serum (>0.5 optical density index) also has diagnostic value, but it has a low sensitivity in the non-neutropenic patient, as it is assumed that the antigen is cleared by circulating neutrophils [22, 23]. Other mycological tests provide suboptimal predictive values: culture on tracheal aspirates and Aspergillus PCR test have good sensitivity but come with more false positives. Emerging data suggest that the galactomannan lateral flow assay (LFA) on BAL fluid may be a viable alternative to enzyme-linked immunosorbent assay (ELISA) galactomannan testing, and could be useful to decrease the time to initiation of antifungal treatment [24]. Repetitive positive mycological tests may add to the certainty of the diagnosis. However, postponing the initiation of antifungal therapy may further compromise survival.

Voriconazole led to better treatment responses and improved survival in comparison to amphotericin B deoxycholate in a randomized controlled trial (RCT), and thus remains the first-line agent for most patients [25]. Posaconazole and isavuconazole have been demonstrated to have similar clinical efficacy to voriconazole in RCTs and can be used as alternatives. All azole antifungals display highly variable pharmacokinetics (especially in ICU patients) [26] and have several drug interactions; furthermore, their plasma levels have been associated with both efficacy and toxicity [27]. Consequently, they require therapeutic drug monitoring (TDM) and dose adjustment [28]. Given that the prevalence of azole-resistance varies across countries, especially in *A. fumigatus*, antifungal susceptibility testing is advised in patients with prior azole exposure or in regions where resistance is endemic [29]. Liposomal amphotericin B is recommended in cases of liver failure or concern over drug–drug interactions, or when TDM for azoles is not available (Fig. 1).

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Data availability
Not applicable.

Declarations

Conflicts of interest
LK has received speaking fees and a research scholarship from BioMérieux, and has been employed by Transgene. SN has received speaking fees from MSD, Pfizer, Biomérieux, Shionogi, Fisher and Peykel, Medtronic, Mundi Pharma. SB has no conflict of interest related to this work.

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